Title: Surgeon age in relation to prognosis after esophageal cancer resection

Running head: Surgeon age and esophagectomy

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MINI-ABSTRACT

This national population-based cohort study suggests surgeon age ≥56 years is associated with increases in both short- and long-term mortality. Individual competency-based assessments may reduce the adverse effects of surgeon aging upon patient outcomes from highly physically and mentally demanding procedures such as esophagectomy.

STRUCTURED ABSTRACT (word count 238)

Objective: It was hypothesized that patient survival improves with increasing surgeon age up to an age where it then decreases.

Background: Experience, and physical and psychological abilities required for esophagectomy may change with increasing surgeon age.

Methods: This population-based cohort study included all patients having undergone esophagectomy for esophageal cancer in Sweden in 1987-2010, with follow-up until 2016. Risk-adjusted cumulative sum (RA-CUSUM) analysis was performed to estimate the relation between surgeon age and 90-day mortality, all-cause and disease-specific 5-year mortality. Change-points in surgeon age identified by the RA-CUSUM were then analyzed in relation to mortality using multivariable Cox regression, providing hazard ratios (HRs) with 95% confidence intervals (CIs), adjusted for age, sex, comorbidity, tumor stage, tumor histology, neoadjuvant therapy, surgeon volume, and calendar year.

Results: Among 139 surgeons performing 1761 esophagectomies, RA-CUSUM analysis of 90-day mortality showed change-points at 43 years (downward deflection) and at 56 years (upward deflection). Both all-cause and disease-specific 5-year mortality had corresponding change-points at 52 years and 56 years. Compared to surgeon age 52–55 years, surgeon age ≤51 years was associated with increased 90-day mortality (HR=1.71, 95%CI 1.01–2.90) and 5-year all-cause mortality (HR=1.21, 95%CI 1.02–1.43), and surgeon age ≥56 years showed increased 90-day mortality (HR=2.38, 95%CI 1.38–4.13), 5-year all-cause mortality (HR=1.29, 95%CI 1.08–1.55), and disease-specific 5-year mortality (HR=1.18, 95%CI 1.01–1.42).

Conclusions: Surgeon age ≤51 and ≥56 years may increase short- and long-term mortality following esophagectomy for cancer.

INTRODUCTION

Esophagectomy is a critical component in the curative treatment of most esophageal cancers. However, this is a technically demanding and time-consuming procedure with higher rates of mortality and morbidity than most other surgical procedures [1–3]. We have previously highlighted the influence of surgeon volume and surgical proficiency gain upon survival from esophageal cancer [4–6], demonstrating the high prognostic value of surgical skill and performance during esophagectomy. The physical and psychological abilities required for this operation may change with increasing surgeon age. Government regulatory bodies often specify the retirement age threshold with a primary emphasis on balancing the workforce, and thus physicians in medical and surgical specialties have a similar retirement age, despite the high technical demands for complex surgery [7,8]. As individual surgeons age their risk-taking behaviour and levels of confidence might change, which may be reflected in surgical practice [9,10]. There is limited evidence of the role of surgeon age on patient outcome from surgery. One previous publication suggested that older surgeon age may negatively influence in-hospital mortality from selected procedures, including pancreatectomy, coronary artery bypass grafting, and carotid endarterectomy [11]. No previous study has examined the influence of surgeon age upon long-term prognosis following any type of cancer surgery. It was hypothesized that the prognosis after esophageal cancer surgery, independent of other prognostic factors, improves with increasing surgeon age up to a certain point as the surgeon gains experience, after which the prognosis declines due to surgeon age-related physical and psychological factors. To test this hypothesis, a Swedish nationwide cohort study with adjustment for potential confounders was conducted.

METHODS

Study design

The comprehensive and well-established nationwide Swedish cohort study utilized for this study has been described in detail elsewhere [4,5]. In brief, the cohort included 98% of all patients with esophageal cancer (adenocarcinoma or squamous cell carcinoma) who underwent esophagectomy between 1987 and 2010 in Sweden, with follow-up until May 31, 2016. Patients with esophageal cancer were identified from the Swedish Cancer Registry, a registry with 98% nationwide coverage of esophageal cancer [12]. Patients who underwent esophagectomy were identified from the Swedish Patient Registry, which has an excellent completeness and high positive identification value (99.6%) for esophageal surgery [13]. The Patient Registry also provided data pertaining to patient medical comorbidities [14]. The comorbidities were classified according to the most up-to-date version of the well-validated Charlson comorbidity score system, where the esophageal cancer diagnosis was not counted [15]. Medical records containing operation notes and histopathological reports were retrieved from all Swedish hospitals where esophageal cancer surgery was performed during the study period. This clinical data collection from the medical records was facilitated through our nationwide Swedish clinical network, established in the mid-1990s [16]. The data retrieval from the medical records followed a predefined study protocol to ensure uniformity, and the reviewers were blinded to the outcome of the patients. Data concerning neoadjuvant therapy, names of the surgeons, date of the operation, tumor pathological stage, and histological subtype were obtained from these individual patient records. The high accuracy of histopathological review of two independent researchers has been previously described [17]. Neoadjuvant therapy was used mainly in more recent years, and when used it was typically a combination of chemotherapy and radiotherapy. Tumor stage was classified according to the TNM classification of the Union Internationale Contre le Cancer (UICC) [18]. Open transthoracic esophagectomy with intrathoracic anastomosis was the dominating procedure (95%). The personal identity number, assigned to each Swedish resident at birth or immigration, enabled linkage of all participants' data between registries and identification of each patient´s medical records. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Exposure

The age of the surgeon at the time of esophagectomy for each patient was the study exposure. This age was calculated from the date of birth of each surgeon and the date of each operation. Surgeon date of birth was identified from the Swedish Matriculation Registry ("Läkarmatrikeln"), which includes all physicians in Sweden. Date of surgery was determined from the operation charts. A previously developed algorithm was used to assign the surgery to the most experienced surgeon whenever more than one surgeon conducted the esophagectomy [4]. First, the primary surgeon's chronological number of surgeries was calculated for each year over the study period. Thereafter, the surgeon with the highest chronological number of surgeries at the index operation was considered responsible for the surgery.

Outcomes

The outcomes were all-cause 90-day and 5-year mortality, as well as disease-specific 5-year mortality, all counted from the date of surgery. The nationwide Swedish Causes of Death Registry provided accurate data for date and causes of death. This Registry has 100% coverage. If a diagnosis of esophageal cancer was listed as a cause of death in this registry, this mortality was defined as disease-specific.

Statistical analysis

Risk-adjusted cumulative sum (RA-CUSUM) curve analysis

RA-CUSUM curves were created to define the proficiency-gain curve for 90-day, 5-year all-cause and disease-specific mortality following esophagectomy [19]. Risk prediction models using logistic regression were employed to calculate the predicted probability of each outcome in each case (the expected survival/mortality). The curves plot the cumulative difference between the observed and expected mortality according to the risk-adjustment model. This was calculated using the CUSUM equation $S_i=S_{i-1}+(\Sigma_i- \Sigma_R); S_0=0$: S_i is the cumulative sum, Σ_i the sum of events at surgeon age i, and Σ_R the sum of expected events at surgeon age i. On the basis of this equation the curve increases if the observed mortality exceeds the expected mortality (downward deflection), and vice versa (upward deflection). Change points were identified as the maximal deflection of the curve from 0. The statistical significance of the change points was analyzed by comparing mortality before and after the change points, using a p-value of less than 0.05 as the level of significance. Potential confounding factors included in the models were age (continuous variable), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or ≥2), pathological tumor stage (0 or I, II, III or IV), tumor histology (adenocarcinoma or squamous cell carcinoma), and use of neoadjuvant therapy (yes or no). Potential confounding factors (surgeon volume and year of surgery) with a strong correlation with the exposure (surgeon age) were not included in this risk adjustment, which is standardized methodology for RA-CUSUM [5]. However given the clinical importance of distinguishing surgeon volume and year of surgery from surgeon age, they were included in the subsequent Cox regression analyses (presented below).

Mann-Whitney U test and Chi-square test

The patients were categorized based on the change points in the surgeon age identified in the RA-CUSUM curve analysis. When comparing patient and tumor characteristics, the continuous variable, patient age, was analyzed using the Mann-Whitney U test, while the binary variables, patient sex, comorbidity, tumor characteristics, utilization of neoadjuvant therapy, reoperation, resection margins and mortality, were compared using the Chi-square test. The level of statistical significance was set at a p-value of less than 0.05.

Kaplan-Meier analysis

Kaplan-Meier survival curve analysis was performed for 5-year all-cause and disease-specific mortality based on the change points identified in the RA-CUSUM curve analysis. When performing the log rank test, a threshold of significance was set at a p-value of less than 0.05.

Cox regression analysis

Finally, the change-points in surgeon age identified by the RA-CUSUM curve analysis were analyzed in relation to the mortality outcomes also using a multivariable Cox-proportional hazards model, providing hazard ratios (HRs) with 95% confidence intervals (CIs). The HRs were adjusted for all six potential confounding factors listed above (with the same categorization) with the addition of cumulative surgeon volume of esophagectomies during study period (≤16 or >16) and calendar period of surgery (year 1987–1994, 1995–2002, or 2003–2010). Cumulative surgeon volume was categorized as ≤16 or >16 esophagectomies based upon the median throughout the study period.

RA-CUSUM curves were computed using Excel (Excel for Mac 2011, version 14.1.4, Microsoft Corporation). For the Mann-Whitney, Chi-square, Kaplan-Meier (with log-rank testing), and Cox regression analysis the SPSS software was used (Statistical Package for the Social Sciences software, Version 22, SPSS Chicago [IL], USA).

RESULTS

Patients and surgeons

The entire cohort included 1820 patients. After excluding 59 patients (3.2%) without the surgeon's age available, 1761 patients remained for final analysis. There was a total of 139 surgeons performing the operations. The median number of esophagectomies performed per surgeon was 16 (range 1-262; interquartile range 6–46).

Surgeon age and change points in mortality

The RA-CUSUM analysis of surgeon age in relation to 90-day mortality showed two change-points, one at 43 years (downward deflection) and another at 56 years (upward deflection) (Figure 1). The association between surgeon age and 5-year all-cause mortality and 5-year disease-specific mortality both showed a first change-point at 52 years (downward deflection) and a second change-point at 56 years (upward deflection) (Figures 2a and 2b). The patients were divided into three groups based upon the change-points for 5-year mortality in surgeon age; ≤51 (patients = 946), 52–55 (patients = 291), or ≥56 (patients = 524) years. There were no major differences between these groups of patients regarding age, sex, comorbidity, tumor stage, tumor histology, utilization of neoadjuvant therapy, reoperation rates, or non-radical (R1/2) resection margins (Table 1). As expected, there was a greater representation of higher volume surgeons in the older surgeon age groups.

Ninety-day mortality

Change-points in surgeon age at 52 years were associated with a reduction in 90-day mortality from 12.1% to 6.9% ($p=0.013$), and an increase in 90-day mortality at 56 years from 6.9% to 12.8% ($p=0.009$). Cox regression analysis demonstrated that compared to surgeon age between 52–55 years (reference category), surgeon age ≤51 years (adjusted HR=1.71, 95%CI 1.01–2.90) and surgeon age ≥56 years (adjusted HR=2.38, 95%CI 1.38–4.13) were associated with increased 90-day mortality (Table 2).

Five-year all-cause mortality

Change-points in surgeon age at 52 years were associated with a reduction in 5-year all-cause mortality from 79.0% to 69.1% ($p<0.001$), and an increase at 56 years from 69.1% to 76.7% ($p=0.017$). The differences in the Kaplan-Meier curves with log-rank test were statistically significant ($p=0.004$) for the three surgeon age groups identified in the RA-CUSUM analysis (Figure 3a). Using surgeon age between 52–55 years as the reference category, surgeon age ≤51 years (HR=1.21, 95%CI 1.02–1.43) and surgeon age ≥56 years (HR=1.29, 95%CI 1.08–1.55) were associated with increased 5-year all-cause mortality.

Five-year disease-specific mortality

Changes in 5-year disease-specific mortality were not statistically significant ($p=0.070$), but followed the same trend in decreasing the mortality in the surgeon age group 52–55 years (60.8%) compared with the ≤51 group (67.4%) and the ≥56 surgeon age group (63.4%). The Kaplan-Meier curves showed a statistical significance in the log-rank test ($p=0.021$) as depicted in Figure 3b. Compared to surgeon age 52–55 years (reference category), surgeon age ≤51 years showed no statistically significant increase (HR=1.14, 95% CI 0.96–1.36), while surgeon age ≥56 years was associated with an increased 5-year disease-specific mortality (HR=1.18, 95% CI 1.01–1.42).

DISCUSSION

The results of this study support the hypothesis under investigation, i.e. that the prognosis after esophageal cancer surgery, independent of other prognostic factors, improves with increasing surgeon age up to a certain point after which the prognosis declines. Among younger surgeons, short-term and long-term mortality are higher as the surgeons gain proficiency, paralleling the results of our previous study [5]. Then, highest surgical competence is achieved between 52 and 56 years of surgeon age. Finally, and most interestingly, both short and long-term mortality are again increased at a surgeon age from 56 years onwards.

The population-based design with nearly complete inclusion of all eligible patients in Sweden is a main strength of the study, along with the complete follow-up of all patients for at least 5 years, and the adjustment for relevant confounding factors, including surgeon volume. The cohort has high accuracy in the identification of patients undergoing esophagectomy for cancer of the esophagus. The relevant data were collected based on a predefined study protocol from extensive review of medical records and nationwide registries, which made it possible to have unbiased and detailed information on exposures, outcomes, and covariates. There are also limitations. The external validity (generalizability) of these findings in another country with a different healthcare structure and surgical training program remains unknown. The median number of esophagectomies per surgeon was low at 16 during the study period, therefore especially for the applicability of these results to high annual volume surgeons remains undetermined by the present study. The study period is long and therefore it is conceivable that developments in other areas over time, e.g. clinical staging, addition of neoadjuvant therapy regimens, and enhanced recovery protocols, may have contributed to the improvement in short- and long-term outcomes. However, year of surgery was adjusted for in the regression model, with the influence of surgeon age persisting. There may be additional unmeasured factors, e.g. new surgical techniques and equipment that may have been used less frequently by older surgeons, but any such differences are not confounders, but rather included as part of the causal pathway for the association between surgeon age and patient prognosis.

A previous retrospective study from the United States suggested that surgeon age did not affect short-term mortality from esophagectomy, however this analysis failed to adjust for tumor stage, use of neoadjuvant therapy, and patient medical comorbidities, and data on long-term survival were not available [11]. The most important finding from the present study is that surgeon age ≥56 years appears to be associated with an increase in patient short- and long-term mortality, paralleling results seen in with younger surgeon age during the early part of their proficiency gain curve [5]. This is unlikely to be an issue associated with changes in patient selection, surgeon volume, or year of surgery as the influence of surgeon age persisted when these factors were adjusted for in the analysis. With age, surgeons gain a greater experience and competence with increasing cumulative surgical volume. However, as with any demanding and time-consuming procedural activity, technical skill and the ability to concentrate for long periods are critical to performing esophagectomy, and both of these may decrease with advancing surgeon age.

Retirement age is most commonly based on the theory that a worker's productivity declines significantly after age 65. However, some occupations that require high levels of physical or mental skill (e.g. airline pilots) often have an earlier retirement age, and retirement might be individual-specific depending on abilities during regular physical and psychological tests [20]. Clearly there is a range of surgeon's physical and psychological ability and some surgeons may perform esophagectomy well past the age of 56 years with excellent outcomes for their patients. However, these first findings of strong associations between older surgeon age and worse long-term survival following esophagectomy for cancer are intriguing, although more studies from other populations are needed before causality can be claimed.

The RA-CUSUM curves (Figure 2a and b) show a continuous improvement in mortality rates until 52, during the period of initial learning, then an average level of performance is reached with some further improvement 52 – 56, and then an actual deterioration in mortality rates beyond 56. Thus the period of optimal performance between 52 – 56 years appears relatively short. However, if an analogy is drawn to other technical performance professions such as athletes or musicians, the level of optimal performance is similarly short, when the professional has sufficient expertise and is at the peak of their technical abilities to maximize their level of performance.

If the results of this study are confirmed they do suggest at a group level there may be a need for a competency-based assessment as surgeons advance in age past 56 years in order to minimize patient harm. Continuous evaluation of surgeon outcomes through a process of national audit is one potential mechanism often utilized to identify a decline in surgical performance [21,22]. However, to identify a measurable change in surgeon performance, patient outcomes will suffer, which ethically is unacceptable. A more robust method may be individual competency-based assessments with human reliability analysis [23–25], which may identify changes in operative performance before such patient harm occurs.

In conclusion, this first study to evaluate changes in mortality as surgeons age increases in performing esophagectomy for cancer indicates that surgeon age ≤51 and ≥56 years is associated with increases in both short- and long-term mortality. These results persisted with adjustment for confounders, indicating an independent prognostic role of surgeon age.

REFERENCES

1. Birkmeyer D, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; **346**: 1128 – 1137.
2. Sahni NR, Dalton M, Culter DM, et al. Surgeon specialization and operative mortality in United States: retrospective analysis. *BMJ* 2016; **354**: i3571
3. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011; **364**: 2128 – 2137.
4. Derogar M, Sadr-Azodi O, Johar A, et al. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. *J Clin Oncol* 2013; **31**: 551 – 557.
5. Markar SR, Mackenzie H, Lagergren P, et al. Surgical proficiency gain and survival after esophagectomy for cancer. *J Clin Oncol* 2016; **34**: 1528 – 1536.
6. Mackenzie H, Markar SR, Askari A, et al. National proficiency-gain curves for minimally invasive gastrointestinal cancer surgery. *Br J Surg* 2016; **103**: 88 – 96.
7. Schenarts PJ, Cemaj S. The aging surgeon: implications for the workforce, the surgeon, and the patient. *Surg Clin North Am* 2016; **96**: 129 – 138.
8. Bhatt NR, Morris M, O'Neil A, et al. When should surgeons retire? *Br J Surg* 2016; **103**: 35 – 42.
9. Ruteledge RB, Smittenaar P, Zeidman P, et al. Risk taking for potential reward decreases across the lifespan. *Curr Biol* 2016; **26**: 1634 – 1639.
10. Josef AK, Richter D, Samanez-Larkin GR, et al. Stability and change in risk-taking propensity across the adult life span. *J Pers Soc Psychol* 2016; **111**: 430 – 450.
11. Waljee JF, Greenfield LJ, Dimick JD, et al. Surgeon age and operative mortality in the United States. *Ann Surg* 2006; **244**: 353 – 362.

12. Lindblad M, Ye W, Lindgren A, et al. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. Ann Surg 2006; 243: 479–485.
13. Lagergren K, Derogar M. Validation of oesophageal cancer surgery data in the Swedish Patient Registry. Acta Oncol 2012; 51: 65–68.
14. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11: 450.
15. Armitage JN, vander Meulen JH, Royal College of Surgeons Co-morbidity Consensus Group. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg 2010; 97: 772–781.
16. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825–831.
17. van der Schaaf M, Johar A, Wijnhoven B, et al. Extent of lymph node removal during esophageal cancer surgery and survival. *J Natl Cancer Inst* 2015; **107**: djv043
18. Sobin LH, Gospodarowicz MK, Wittekind C. UICC TNM classification of malignant tumors, 6th edition. Wiley Blackwell; 2009.
19. Grigg OA, Farewell VT, Spiegelhalter DJ. Use of risk-adjusted CUSUM and RSPRT charts for monitoring in medical contexts. *Stat Methods Med Res.* 2003; **12**: 147-170.
20. http://www.caa.co.uk/medical/ [last accessed 02-12-16]

21. Chadwick G, Riley S, Hardwick RH, et al. Population-based cohort study of the management and survival of patients with early-stage oesophageal adenocarcinoma in England. *Br J Surg* 2016; **103**: 544 – 552.

22. Visser E, van Rossum PS, Leeftink AG, et al. Impact of diagnosis-to-treatment waiting time on survival in esophageal cancer patients – a population-based study in the Netherlands. *Eur J Surg Oncol* 2016. PMID: 27847286.

23. Miskovic D, Ni M, Wyles SM, et al. Observational clinical human reliability analysis (OCHRA) for competency assessment in laparoscopic colorectal surgery at the specialist level. *Surg Endosc* 2012; **26**: 796 – 803.

24. Ahmed AR, Miskovic D, Vijayaseelan T, et al. Root cause analysis of internal hernia and Roux limb compression after laparoscopic Roux-en-Y gastric bypass using observation clinical human reliability assessment. *Surg Obes Relat Dis* 2012; **8**: 158 – 163.

25. Talebpou M, Alijani A, Hanna GB. Proficiency-gain curve for an advanced laparoscopic procedure defined by observation clinical human reliability assessment (OCHRA). *Surg Endosc* 2009; **23**: 869 – 875.

FIGURE LEGENDS

Figure 1. RA-CUSUM curve for 90-day all-cause mortality, showing change-points at surgeon ages of 43 (downward deflection) and 56 years (upward deflection).

Figure 2a. RA-CUSUM curve for 5-year all-cause mortality, showing change-points at surgeon ages of 52 (downward deflection) and 56 years (upward deflection).

Figure 2b. RA-CUSUM curve for 5-year disease-specific mortality, showing change-points at surgeon ages of 52 (downward deflection) and 56 years (upward deflection).

Figure 3a. Kaplan-Meier survival curve analysis for 5-year all-cause mortality and the three surgeon age groups; ≤51, 52–55, and ≥56 years (chi-square=11.29, p=0.004).

Figure 3b. Kaplan-Meier survival curve analysis for 5-year disease-specific mortality and the three surgeon age groups; ≤51, 52–55, and ≥56 years (chi-square=7.70, p=0.021).